

B62

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
27 May 2004 (27.05.2004)

PCT

(10) International Publication Number
WO 2004/043984 A1

(51) International Patent Classification⁷: C07H 17/08,
17/00, A61K 31/7048, A61P 31/04

28, HR-10000 Zagreb (HR). BRAJSA, Karmen [HR/HR];
Jablanska 42, HR-10000 Zagreb (HR).

(21) International Application Number:
PCT/HR2003/000057

(74) Common Representative: PLIVA D.D.; Pravni
Poslovi-Intelektualno vlasnistvo, Povrzenic, Nives,
Ulica grada Vukovara 49, HR-10000 Zagreb (HR).

(22) International Filing Date:
10 November 2003 (10.11.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data:
P20020886A 11 November 2002 (11.11.2002) HR

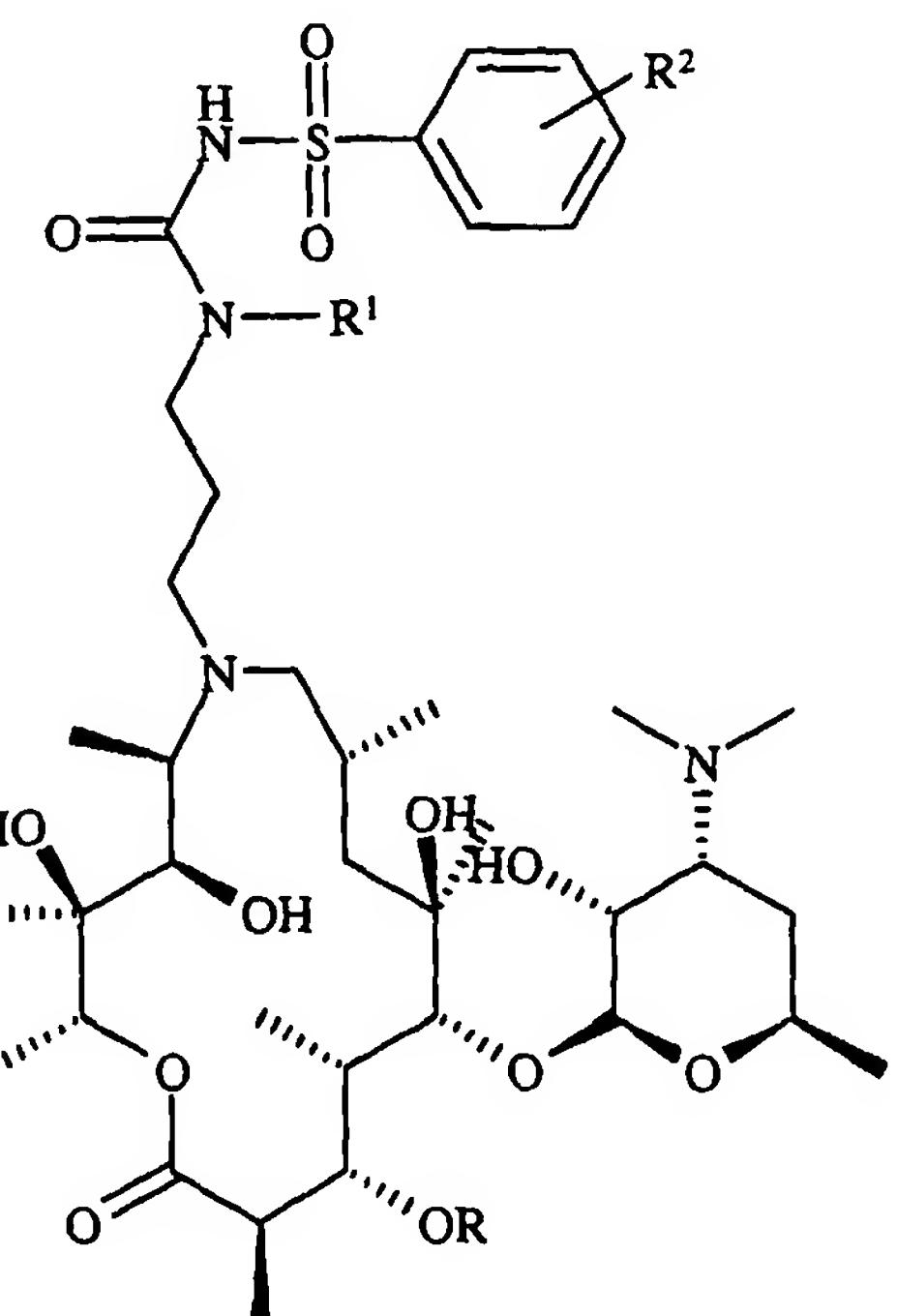
(84) Designated States (*regional*): ARIPO patent (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant and
(72) Inventor (*for all designated States except US*): PLIVA
D.D. [HR/HR]; Ulica grada Vukovara 49, HR-10000 Za-
greb (HR).
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): KUJUNDZIC, Ned-
jeljko [HR/HR]; Slavenskog 4, HR-10000 Zagreb (HR).
BUKVIC KRAJACIC, Mirjana [HR/HR]; Tjardoviceva

Published:
— with international search report

[Continued on next page]

(54) Title: SUBSTITUTED 9a-N-[N'-(BENZENESULFONYL)CARBAMOYL-Y-AMINOPROPYL]AND 9a-N-[N'-(B-CYA-
NEOTHYL)-N'-(BENZENESULFONYL)CARBAMOYL-Y-AMINOPROPYL]DERIVATIVES OF 9-DEOXO-9-DIHY-
DRO-9A-AZA-9A-HOMOERITHROMYCIN A AND 5-O-DESOSAMINYL-9-DEOXO-9-DIHYDRO-9A-AZA-HO-
MOERITHRONOLIDE A



(57) Abstract: The invention relates to substituted 9a-N-[N'-(benzenesulfonyl)carbamoyl-γ-aminopropyl] and 9a-N-[N'-(β-cyanoethyl)-N'-(benzenesulfonyl)carbamoyl-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series, of the formula (I) wherein R represents H or cladinosyl moiety, R¹ represents H or β-cyanoethyl group and R² represents H or fluoro, chloro and methyl group, and pharmaceutically acceptable salts thereof with inorganic or organic acids, to the process for the preparation of pharmaceutical compositions as well as to the use their compositions for sterilization rooms and medical instruments as well as for protection of wall and wooden coatings.

WO 2004/043984 A1



- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

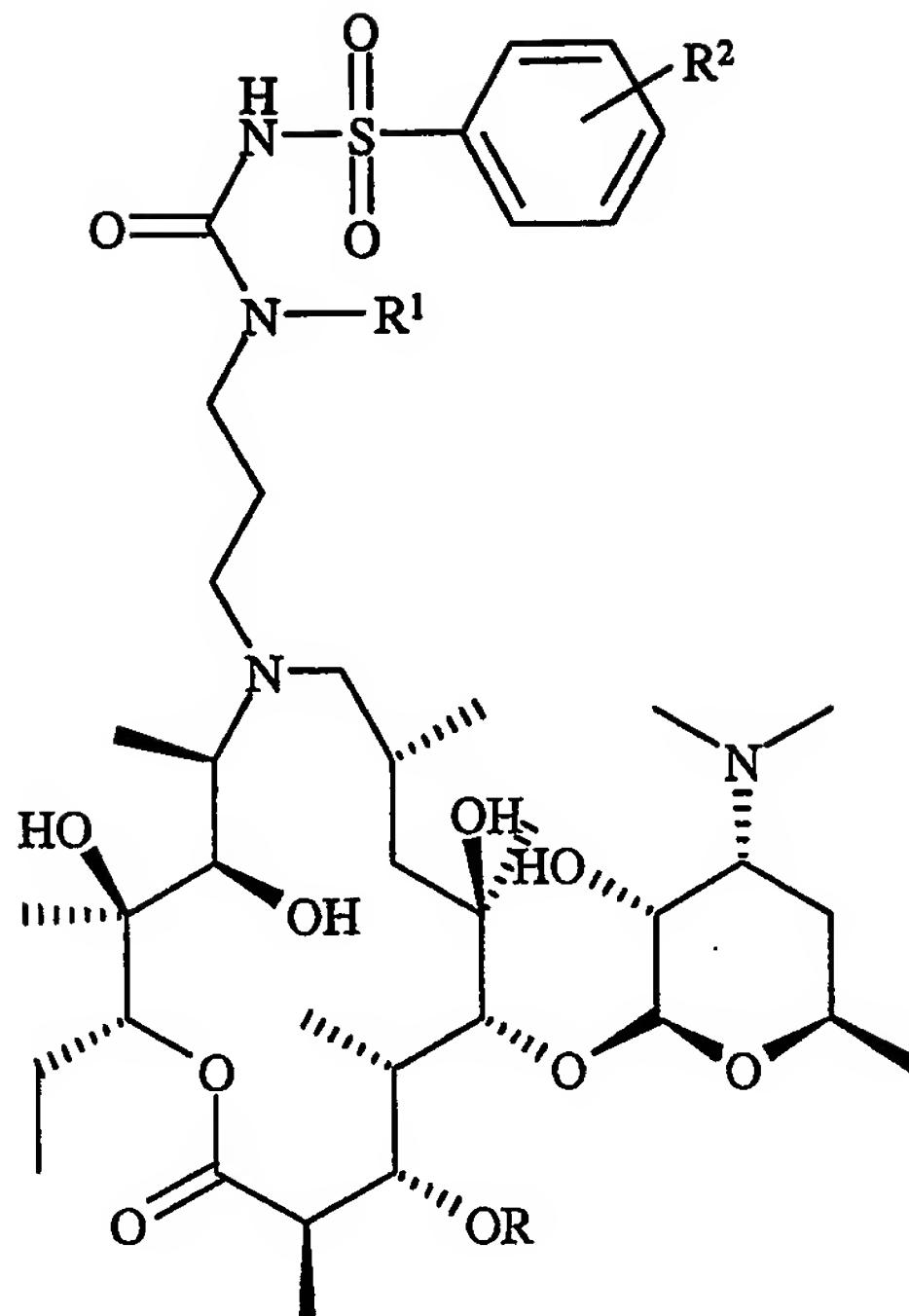
**Substituted 9a-N-[N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] and
9a-
-N-[N'-(β -cyanoethyl)-N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl]
derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and
5-O-
-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A**

Technical field

Int. Cl. C 07H 17/08, A61K 31/71

Technical Problem

The present invention relates to substituted 9a-N-[N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series having antibacterial activity, general formula 1,



wherein R represents H or cladinosyl moiety, R¹ represents H or β-cyanoethyl group and R² represents H or fluoro, chloro and methyl group, to pharmaceutically acceptable addition salts thereof with inorganic or organic acids, to a process for the preparation of the pharmaceutical compositions as well as to the use of these compositions for the sterilization the rooms and the medicinal instruments, as well as for the prevention of walls and wooden materials.

Prior Art

Erythromycin A is a macrolide antibiotic, whose structure is characterized by 14-membered macrolactone ring having carbonyl group in C-9 position. It was found by McGuire in 1952 [*Antibiot. Chemother.*, 2 (1952) 281] and for over 40 years it has been considered as a reliable and effective antimicrobial agent in the treatment of diseases caused by Gram-positive and some Gram-negative microorganisms. However, in an acidic medium it is easily converted into anhydroerythromycin A, an inactive C-6/C-12 metabolite of a spiroketal structure [P. Kurath et al., *Experientia* 27 (1971) 362]. It is well-known that spirocyclisation of aglycone ring of erythromycin A is successfully inhibited by a chemical transformation of C-9 ketones or hydroxy groups in C-6 and/or

C-12 position. By the oximation of C-9 ketones [S. Đokić et al., *Tetrahedron Lett.* **1967**: 1945] and by subsequently modifying the obtained 9(E)-oxime into 9-[O-(2-methoxyethoxy)methyloxime]erithromycin A (ROXITHROMYCIN) [G. S. Ambrieres, Fr. pat. 2,473,525, 1981] or 9(S)-erithromycylamine [R. S. Egan et al., *J. Org. Chem.* **39** (1974) 2492] or a more complex oxazine derivative thereof, 9-deoxo-11-deoxy-9,11-{imino[2-(2-methoxyethoxyethylidene]oxy}-9(S)-erythromycin A (DIRITHROMYCIN) [P. Lugar et al., *J. Crist. Mol. Struct.* **9** (1979) 329], novel semisynthetic macrolides were synthetized, whose basic characteristic, in addition to a greater stability in an acidic medium, is a better pharmacokinetics and a long half-time with regard to the parent antibiotic erythromycin A. In a third way for modifying C-9 ketones use is made of Beckmann rearrangement of 9(E)-oxime and of a reduction of the obtained imino ether (G. Kobrehel et al., U.S. Pat. 4,328,334, 1982.) into 11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9a-aza-9a-homoerythromycin A) under broadening the 14-member ketolactone ring into a 15-member azalactone ring. By reductive N-methylation of 9a-amino group according to Eschweiler-Clark process (G. Kobrehel et al., BE Pat. 892,397, 1982.) or by a preliminary protection of amino group by means of conversion into the corresponding N-oxides and then by alkylation and reduction [G. M. Bright, U.S. Pat., 4,474,768, 1984.] N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9a-methyl-9a-aza-9a-homoerithromycin A, AZITHROMYCIN) was syntetized, a prototype of azalide antibiotics, which, in addition to a broad antimicrobial spectrum including Gram-negative bacteria and intracellular microorganisms, are characterized by a specific mechanism of transport to the application site, a long biological half-time and a short therapy period. In EP A 0316128 (Bright G. M. et al.) novel 9a-allyl and 9a-propargyl derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A are disclosed and in U.S. Pat. 4,492,688, from 1985 (Bright G. M.) the synthesis and the antibacterial activity of the corresponding cyclic ethers are disclosed. In the there are further disclosed the synthesis and the activity spectrum of novel 9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamates and O-methyl derivatives thereof (G. Kobrehel et al., *J. Antibiot.* **46** (1993) 1239-1245).

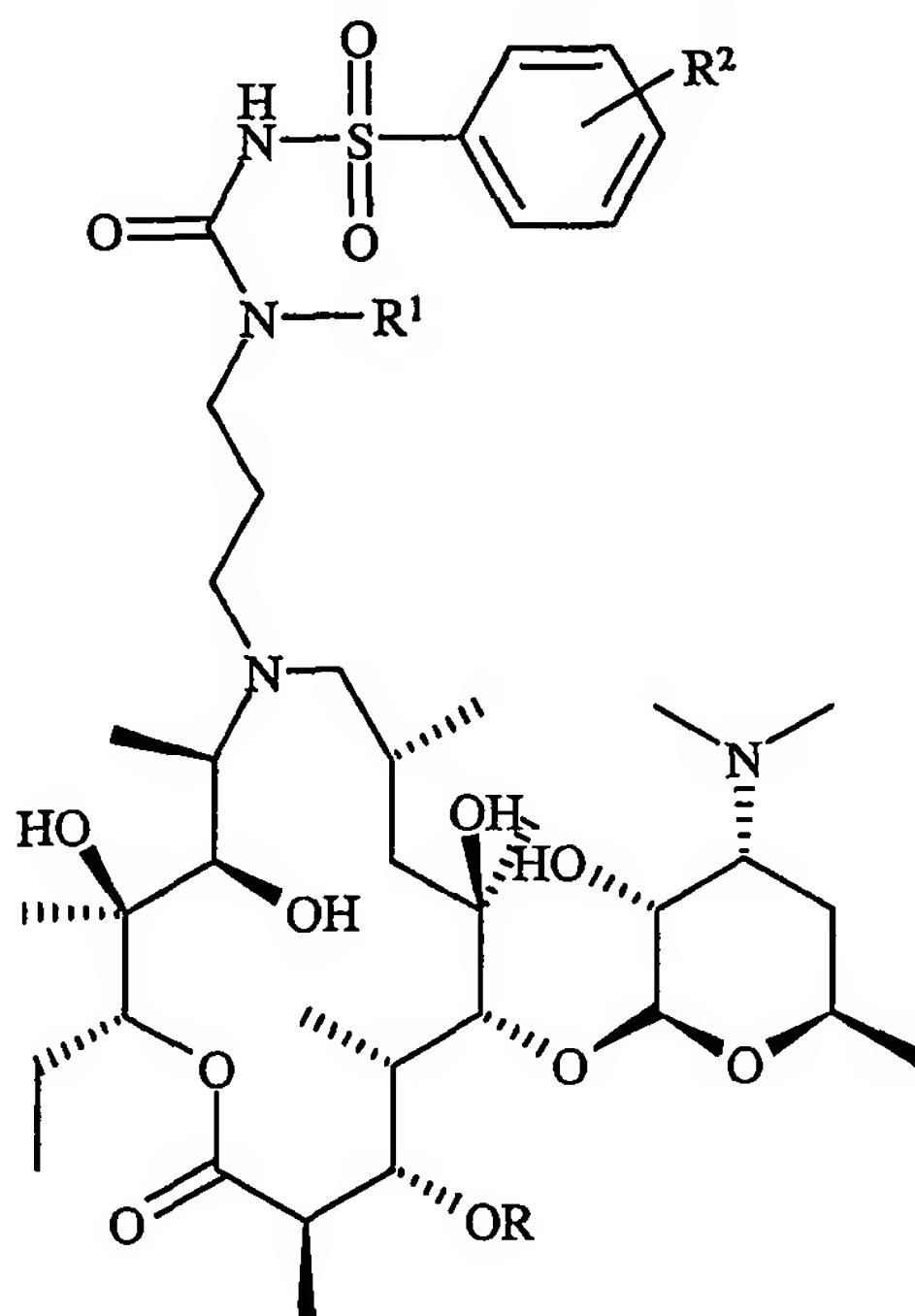
By reaction of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A with isocyanates or isothiocyanates respectively [N. Kujundžić et al. Croat. Pat. 931480, 1993.], 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A with a certain antibacterial activity are obtained.

According to the known and established Prior Art, 9a-N-[N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, a process for the preparation thereof as well as the preparation methods and use of pharmaceutical preparations have not been disclosed as yet.

It has been found and it is object of the present invention, that 9a-N-[N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series and pharmaceutically acceptable addition salts thereof with inorganic or organic acids may be prepared by reacting 9a-N-(γ -aminopropyl) or 9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A with phenylsulfonylisocyanate and optionally by reacting the obtained 9a-N-[N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A with inorganic and organic acids.

Technical Solution

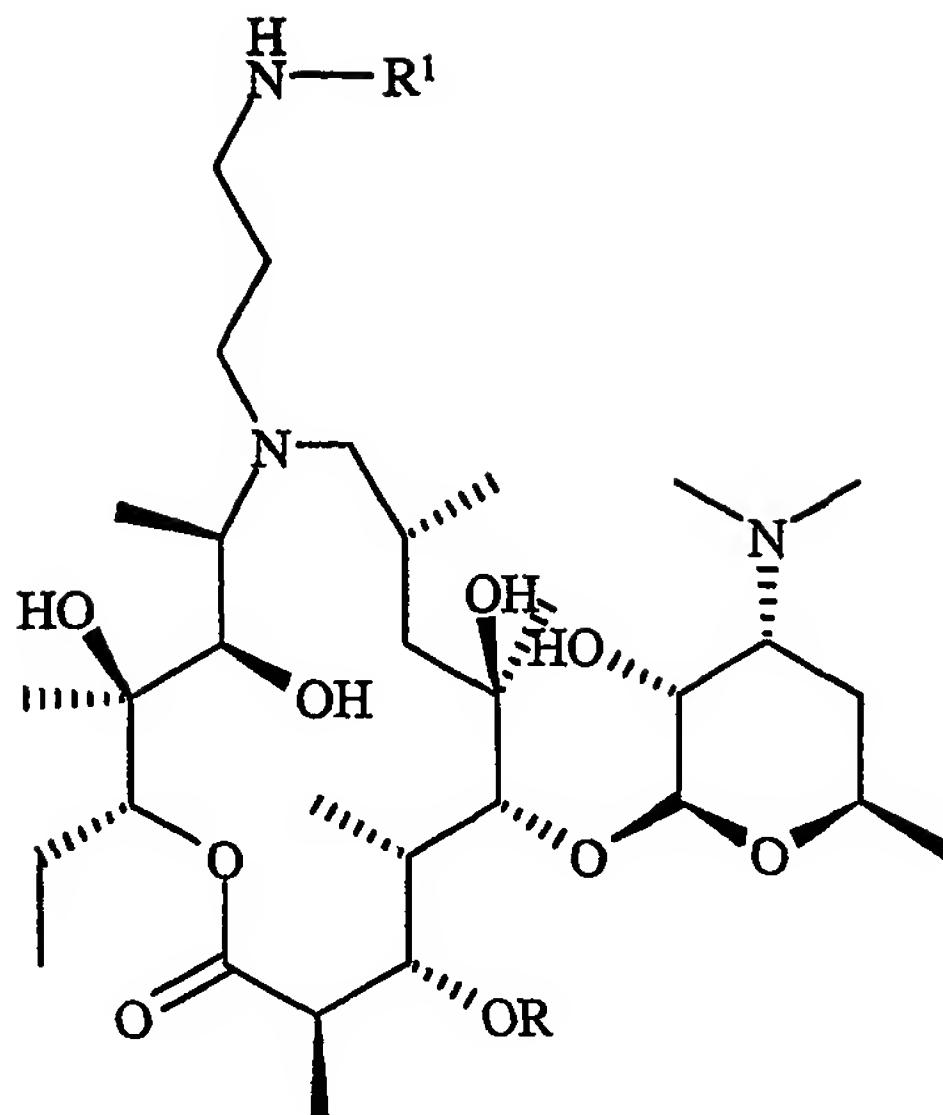
It has been found that novel 9a-N-[N'-(benzenesulfonyl)carbamoyl-(N'-benzenesulfonyl)carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-benzenesulfonyl)carbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homo-erithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula 1, wherein R represents H or cladinosyl group, R¹ represents H or β -cyanoethyl moiety and R² represents H or fluoro, chloro and methyl group



1

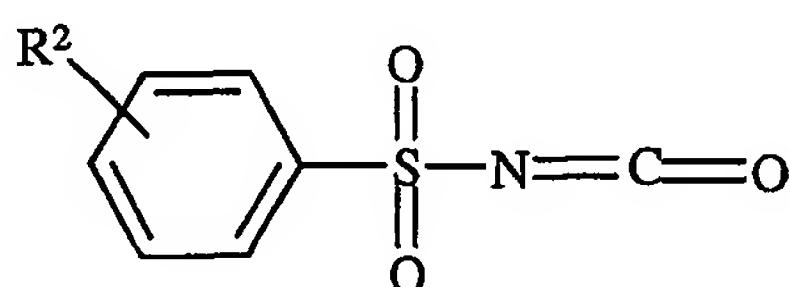
may be prepared by reacting 9a-N-(γ -aminopropyl) and 9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-

-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A general formula 2,



2

wherein R represents H or cladinosyl group and R¹ represents H or β-cyanoethyl moiety, with the substituted phenylsulfonylisocyanates general formula 3,



3

wherein R² represents H or fluoro, chloro and methyl group, in toluene, xylene or some other aprotic solvent, at a temperature 0° to 110°C.

Pharmaceutically acceptable acid addition salts, which also represents an object of the present invention are obtained by reacting 9a-N-[N'-(benzenesulfonyl)carbamoyl-γ-aminopropyl] and 9a-N-[N'-(β-cyanoethyl)-N'-(benzenesulfonyl)carbamoyl-γ-aminopropyl] derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A with an at least equimolar amount of the corresponding inorganic or organic acid such as hydrochloric acid, hydroiodic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, propionic acid, benzoic acid, benzene sulfonic acid, methane sulfonic acid, lauryl sulfonic acid, stearic acid, palmitic acid,

succinic acid, ethylsuccinic acid, lactobionic acid, oxalic acid, salicylic acid and similar acid, in a solvent inert to the reaction. Addition salts are isolated by evaporating the solvent or, alternatively, by filtration after a spontaneous precipitation or a precipitation by the addition of a non-polar cosolvent.

9a-N-[N'-(Benzenesulfonyl)carbamoyl- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homo-erithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula **1** and pharmaceutically acceptable addition salts with inorganic or organic acids thereof possess an antibacterial activity *in vitro*.

Minimal inhibitory concentration (MIC) is defined as the concentration which shows 90% growth inhibition, and was determinated by broth dilution methods National Committe for Clinical Laboratory Standards (NCCLS, M7-A2 protocols). Final concentration of test substances were in range from 64 to 0.125 mg/l. MIC levels for all compound were determinated on panel of susceptible and resistant Gram positive bacterial strains (*S. aureus*, *S. pneumoniae* and *S. pyogenes*) and on Gram negative strains (*E. coli*, *H. influenzae*, *E. faecalis*, *M. catarrhalis*).

Test substances from Examples 1 to 7 and 15 to 21 were active on susceptible strains of *S. pyogenes* (MIC 0.125 to 4.0 mg/l), and on susceptible strains on *S. pneumoniae* (MIC 0.125 to 8.0 mg/l). MIC values on susceptibile *S. aureus* strains were from 1 to 16 mg/l. Substances from Examples 1 to 7 and 15 to 21 showed strong antimicrobial activities on most tested Gram negative strains; *M. catarrhalis* MIC from 0.25 to 16 mg/l, *E. coli* from 8 to 16 mg/l, *E. faecalis* from 2 to 8 mg/l.

The obtained results for substances from Example 1 to 7 and 15 to 21 expressed as MIC in mg/l suggest a potential use thereof as sterilization agents of e.g. rooms and medical instruments and as industrial microbial agents e. g. for the protection of wall and wooden coatings.

Process for the preparation of 9a-N-[N'-(benzenesulfonylcarbamoyl)- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl] derivatives of 9-deoxo-9-

-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-

-homoerithronolide A of this invention is illustrated by the following Examples which should in no way be construed as a limitation of the scope thereof.

Example 1**9-Deoxo-9-dihydro-9a-N-[N'-(p-toluensulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A**

A mixture of 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.26 g (1.3 mmol) of p-toluensulfonylisocyanate in 30 ml dry toluene was stirred for on 1.0 hour at the temperature 0-5 °C to complete the reaction. The crystals of the crude product were filtered, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol = 7 : 3, pure 9-deoxo-9-dihydro-9a-N-[N'-(p-

-toluensulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 989.

Example 2**9-Deoxo-9-dihydro-9a-N-[N'-(4-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A**

From 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.28 g (1.3 mmol) of 4-chlorobenzenesulfonylisocyanate in 20 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol = 1 : 1, pure 9-deoxo-9-dihydro-9a-N-[N'-(4-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1009.

Example 3**9-Deoxo-9-dihydro-9a-N-[N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A**

From 1.01 g (1.28 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.23 g (1.91 mmol) of benzenesulfonylisocyanate in 20 ml dry

toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol = 1 : 1, pure 9-deoxo-9-dihydro-9a-N-[N'-(benzenesulfonyl)-carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 975.

Example 4

9-Deoxo-9-dihydro-9a-N-[N'-(o-toluenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

From 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-(γ -aminopropyl)-9a-homoerithromycin A and 0.26 g (1.3 mmol) of o-toluensulfonylisocyanate in 20 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol = 1 : 1, pure 9-deoxo-9-dihydro-9a-N-[N'-(o-toluensulfonyl)-carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 989.

Example 5

9-Deoxo-9-dihydro-9a-N-[N'-(2-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

From 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-aza-9a-N-(γ -aminopropyl)-9a-homoerithromycin A and 0.28 g (1.3 mmol) of 2-chlorobenzenesulfonylisocyanate in 20 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol = 7 : 3, pure 9-deoxo-9-dihydro-9a-N-[N'-(2-

-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1009.

Example 6

9-Deoxo-9-dihydro-9a-N-[N'-(4-fluorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

From 1.0 g (1.26 mmol) 9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-9a-homoerithromycin A and 0.28 g (1.3 mmol) of 4-fluorobenzenesulfonylisocyanate in 20 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol = 7 : 3, pure 9-deoxo-9-dihydro-9a-N-[N'-(4-

-fluorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 993.

Example 7

5-O-Desozaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-9a-homoerithronolide A

The suspension of 10.0 g (12.6 mmol) 9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-9a-homoerithromycin A 120 ml of hydrochloric acid (10 %) was stirred for 24 hours at a room temperature, the pH was adjusted to 9.5 – 10 by adding 5 N sodium hydroxide solution and was extracted with methylene chloride (3 x 40 ml). The combined organic layers was washed with water (2 x 50 ml), dried over anhydrous sodium sulfate, evaporated to dryness under reduced pressure to give crude product wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol = 7 : 3, pure 5-O-desozaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 653.

Exemple 8**5-O-DesozaminyI-9-deoxo-9-dihydro-9a-N-[N'- (p-toluenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A**

From 1.0 g (1.26 mmol) 5-O-desozaminyI-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-

-9a-homoerithronolide A and 0.34 g (1.73 mmol) of p-toluenesulfonylisocyanate in 20 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : 25% ammonia = 90 : 20 : 1.5, pure 5-O-desozaminyI-9-deoxo-9-dihydro-9a-N-[N'- (p-toluenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 831.

Example 9**5-O-DesozaminyI-9-deoxo-9-dihydro-9a-N-[N'- (4-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A**

From 1.0 g (1.57 mmol) 5-O-desozaminyI-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-

-9a-homoerithronolide A and 0.36 g (1.765 mmol) of 4-chlorobenzenesulfonylisocyanate in 20 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : 25% ammonia = 90 : 20 : 1.5, pure 5-O-desozaminyI-9-deoxo-9-dihydro-9a-N-[N'- (4-chlorobenzenesulfonyl)- carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 851.

Example 10**5-O-Desozaminyl-9-deoxo-9-dihydro-9a-N-[N'-(4-fluorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A**

From 1.0 g (1.57 mmol) 5-O-desozaminyl-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-9a-homoerithronolide A and 0.35 g (1.73 mmol) of 4-fluorobenzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : 25% ammonia = 90 : 20 : 1,5 pure 5-O-desozaminyl-9-deoxo-9-dihydro-9a-N-[N'-(4-fluorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 835.

Example 11**5-O-Desozaminyl-9-deoxo-9-dihydro-9a-N-[N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A**

From 1.0 g (1.57 mmol) 5-O-desozaminyl-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-9a-homoerithronolide A and 0.30 g (1.65 mmol) of benzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : 25% ammonia = 90 : 20 : 1,5, pure 5-O-desozaminyl-9-deoxo-9-dihydro-9a-N-[N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 817.

Example 12**5-O-Desozaminyl-9-deoxo-9-dihydro-9a-N-[N'-(o-toluenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A**

From 1.0 g (1.57 mmol) 5-O-desozaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-

-9a-homoerithronolide A and 0.33 g (1.65 mmol) of o-toluenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherfrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : 25% ammonia = 90 : 20 : 1.5, pure 5-O-desozaminy-9-deoxo-9-dihydro-9a-N-[N'-(p-toluenesulfonyl)carbamoyl- γ -amino- propyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 831.

Example 13

5-O-Desozaminy-9-deoxo-9-dihydro-9a-N-[N'-(2-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

From 1.0 g (1.57 mmol) 5-O-desozaminy-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-

-9a-homoerithronolide A and 0.33 g (1.65 mmol) of 2-chlorobenzenesulfonylisocyanate in 25 ml dry xylene the crude product was obtained, wherfrom by chromatography on silica gel column using the solvent system methylene-chloride : methanol : 25% ammonia = 90 : 20 : 1.5, pure 5-O-desozaminy-9-deoxo-9-dihydro-9a-N-[N'-(2-chlorobenzenesulfonyl)carba- moyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 851.

Example 14

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

The solution of 10.0 g (15.7 mmol) 9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-9a-

-homoerithromycin A and 1.0 ml (18.0 mmol) acrylonitrile in 200 ml methanola was heated at the boiling temperature for a 10 hours and evaporated to drieness and the crude product was obtained where from by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5 pure 9-deoxo-9-dihydro-9a-N-

-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 877.

Example 15

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(p-toluenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

From 1.0 g (1.18 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-

-9a-homoerithromycin A and 0.25 g (1.25 mmol) of p-toluenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherfrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(p-toluenesulfonyl)carbamoyl- γ -aminopropyl]-

-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1042.

Example 16

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(o-toluenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

From 1.0 g (1.18 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-

-9a-homoerithromycin A and 0.25 g (1.25 mmol) of o-toluenesulfonylisocyanate in 25

ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia =

90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(o-toluenesulfonyl)carbamoyl- γ -aminopropyl]-

-9a-aza-9a-homoerithromycin A was obtained.

MS(ES⁺)m/z = 1042.

Example 17

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(4-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

From 1.0 g (1.18 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-

-9a-homoerithromycin A and 0.27 g (1.25 mmol) of 4-chlorobenzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(4-chlorobenzenesulfonyl)carbamoyl- γ -

-aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.
MS(ES⁺)m/z = 1051.

Example 18

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

From 1.0 g (1.18 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-

-9a-homoerithromycin A and 0.27 g (1.25 mmol) of 2-chlorobenzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on

silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.
MS(ES⁺)m/z = 1051.

Example 19

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

From 1.0 g (1.18 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.23 g (1.25 mmol) of benzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(benzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.
MS(ES⁺)m/z = 1028.

Example 20

9-Deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(4-fluorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A

From 1.0 g (1.18 mmol) 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithromycin A and 0.25 g (1.25 mmol) of 4-fluorobenzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 %

ammonia = 90 : 9 : 1.5, pure 9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(4-fluorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithromycin A was obtained.
MS(ES⁺)m/z = 1014.

Example 21

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

The solution of 10.0 g (15.7 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-(γ -aminopropyl)-9a-aza-9a-homoerithronolide A and 0.8 ml (15.7 mmol) acrylonitrile in 200 ml methanole was heated at the boiling temperature for a 10 hours and evaporated to dryness and the crude product was obtained wherefrom by chromatography on silica gel column using the solvent system methylen chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 688.

Example 22

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(p-toluenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

From 1,0 g (1,46 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithronolide A and 0,31 g (1,55 mmol) of p-toluenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-

-(β -cyanoethyl)-N'-(p-toluenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronoli- de A was obtained.

MS(ES⁺)m/z = 883.

Example 23

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(4-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

From 1.0 g (1.46 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -

-aminopropyl]-9a-aza-9a-homoerithronolide A and 0.36 g (1.65 mmol) of 4-chlorobenzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-

-9a-N-[N'-(β -cyanoethyl)-N'-(4-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-

-homoerithronolide A was obtained.

MS(ES⁺)m/z = 889.

Example 24

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)-N'-(2-chlorobenzene-sulfonyl)carbamoyl- γ -aminopropyl]-9a-aza-9a-homoerithronolide A

From 1.0 g (1.46 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β -cyanoethyl)- γ -aminopropyl]-9a-aza-9a-homoerithronolide A and 0.36 g (1.65 mmol) of 2-chlorobenzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-

-9a-N-[N'-(β -cyanoethyl)-N'-(2-chlorobenzenesulfonyl)carbamoyl- γ -aminopropyl]-9a-

aza-9a-

-homoerithronolide A was obtained.

MS(ES⁺)m/z = 889.

Example 25

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(o-toluenesulfonyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A

From 1.0 g (1.46 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-γ-

-aminopropyl]-9a-aza-9a-homoerithronolide A and 0.31 g (1.55 mmol) of o-toluenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'

-(β-cyanoethyl)-N'-(o-toluenesulfonyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 884.

Example 26

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(benzenesulfonyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A

From 1.0 g (1.46 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-γ-

-aminopropyl]-9a-aza-9a-homoerithronolide A and 0.36 g (1.65 mmol) of benzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'

-(β-cyanoethyl)-N'-(benzenesulfonyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 870.

Example 27

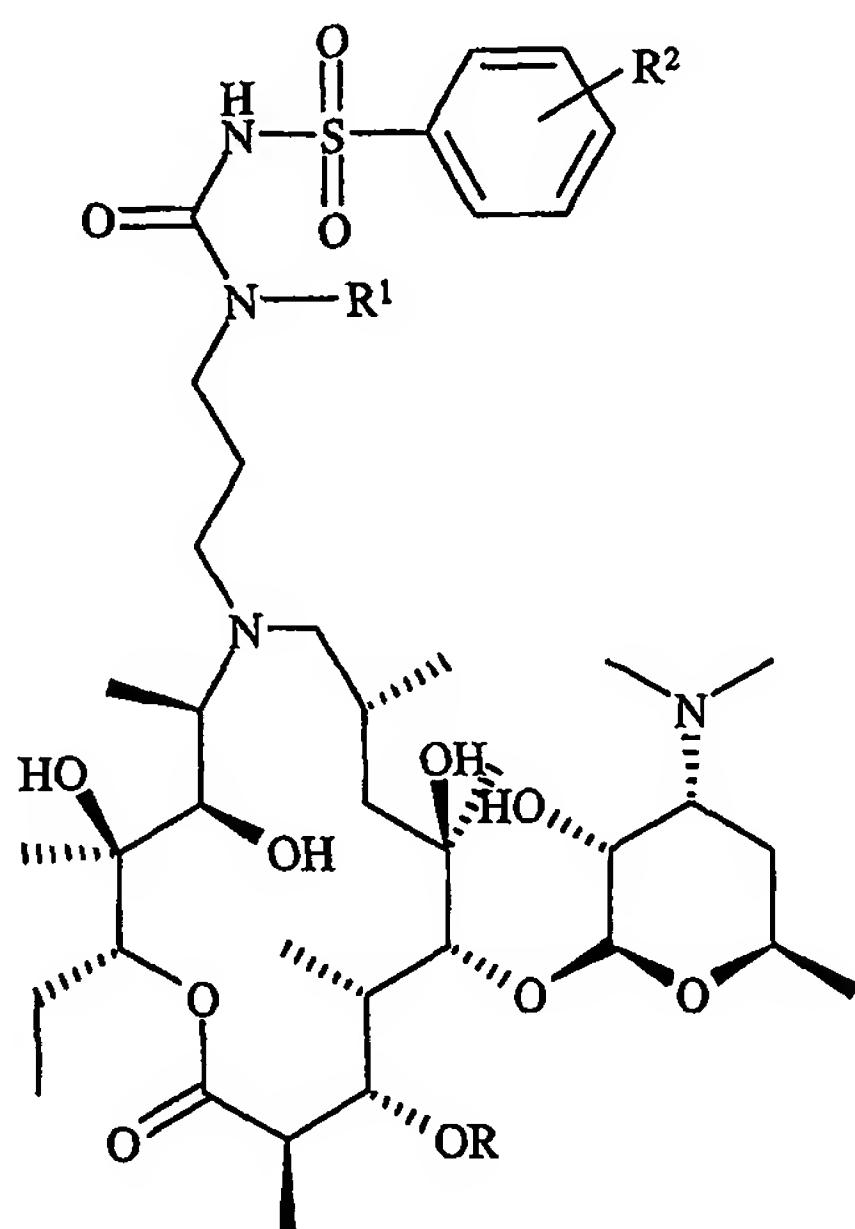
5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(4-fluorobenzenesulfonyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A

From 1.0 g (1.46 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-γ-aminopropyl]-9a-aza-9a-homoerithronolide A and 0.36 g (1.65 mmol) of 4-fluorobenzenesulfonylisocyanate in 25 ml dry toluene the crude product was obtained, wherefrom by chromatography on silica gel column using the solvent system methylene chloride : methanol : 25 % ammonia = 90 : 9 : 1.5, pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(β-cyanoethyl)-N'-(4-fluorobenzenesulfonyl)carbamoyl-γ-aminopropyl]-9a-aza-9a-homoerithronolide A was obtained.

MS(ES⁺)m/z = 888.

CLAIMS

1. Substituted 9a-N-[N'-(benzenesulfonylcarbamoyl)- γ -aminopropyl] and 9a-N-[N'-(β -cyanoethyl)-N'-(benzenesulfonyl)- γ -aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminy-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series having antibacterial action of the general formula 1,



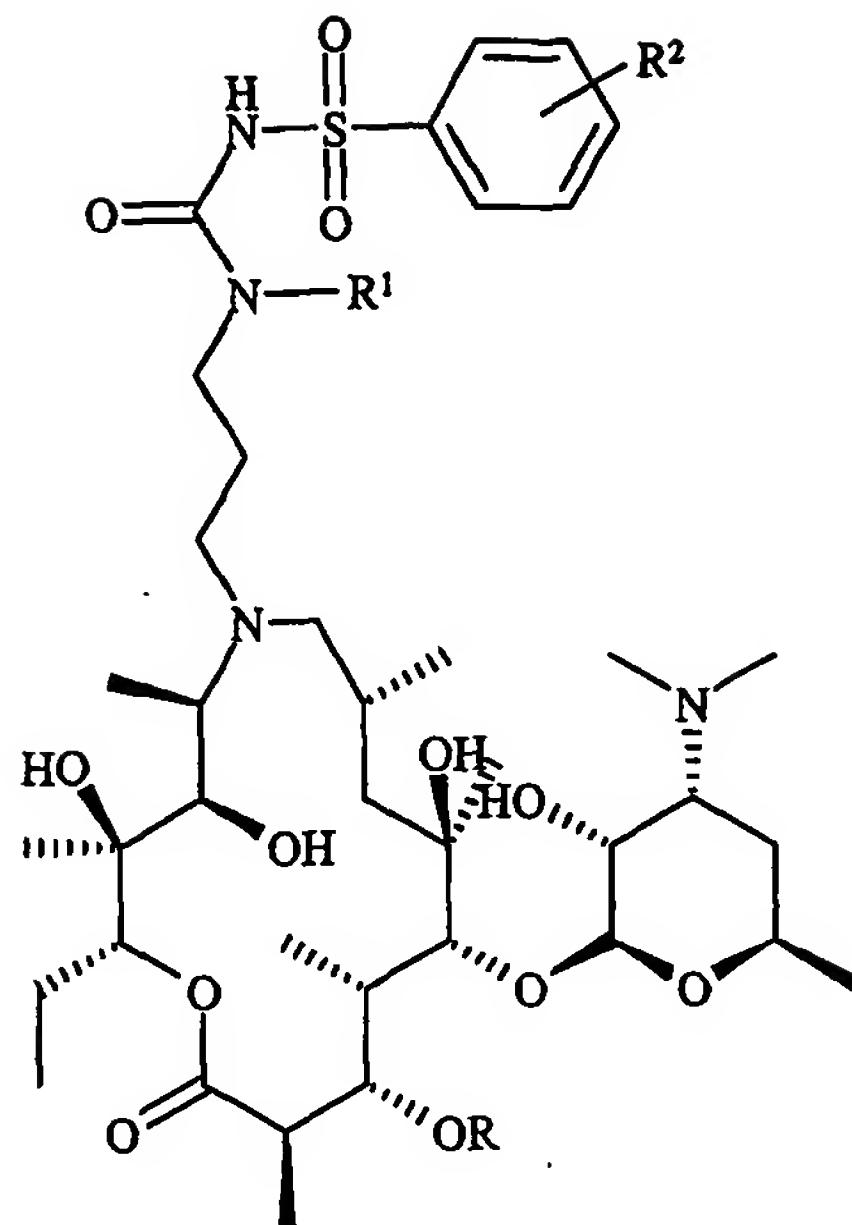
1

wherein R represents H or cladinosyl moiety, R¹ represents H or β -cyanoethyl moiety and R² represents H or fluoro, chloro and methyl group and pharmaceutically acceptable addition salts thereof with inorganic or organic acids.

2. Substance according to claim 1, characterized in that R represents cladinosyl group and R¹ = R² represent H.

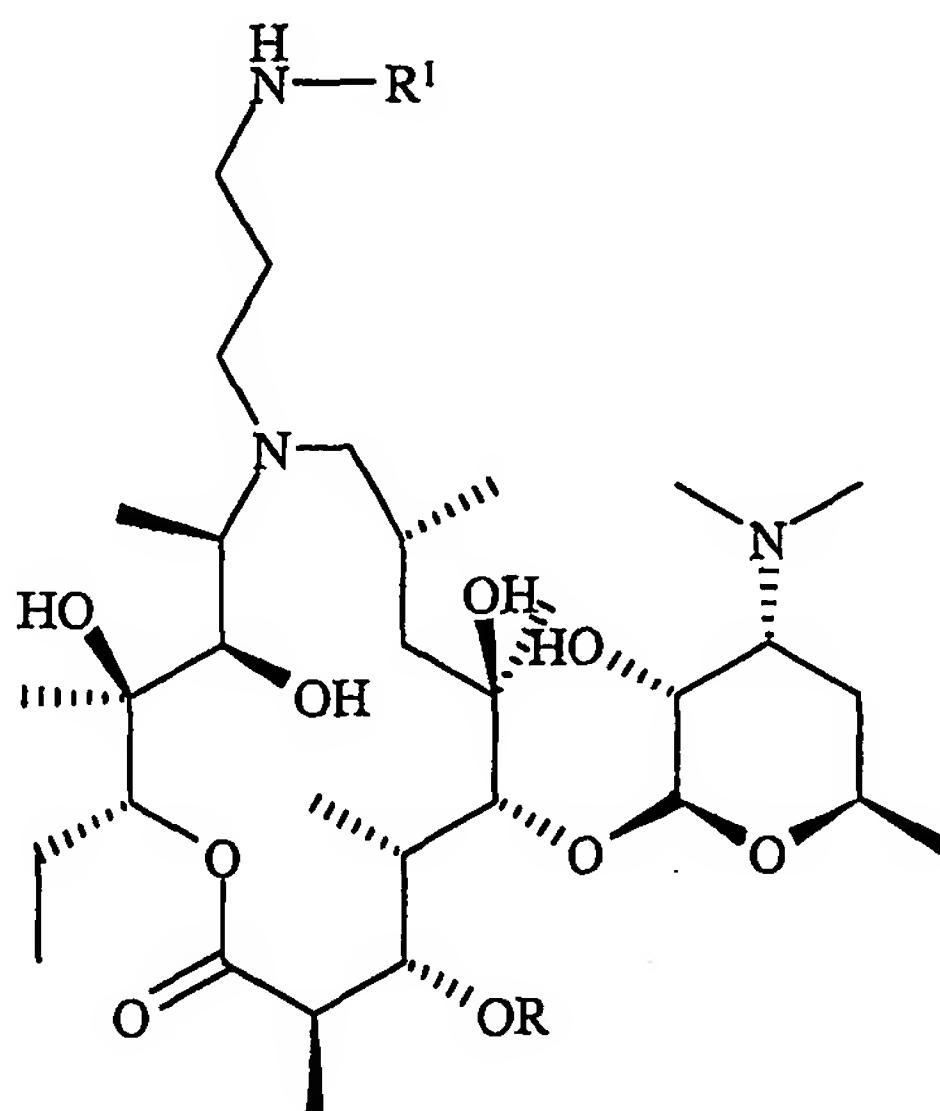
3. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 4-chloro group.
4. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 2-chloro group.
5. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 4-fluoro group.
6. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 4-methyl group.
7. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents H and R² represents 2-methyl group.
8. Substance according to claim 1, characterized in that R = R¹ = R² represent H.
9. Substance according to claim 1, characterized in that R = R¹ represent H and R² represents 4-chloro group.
10. Substance according to claim 1, characterized in that R = R¹ represent H and R² represents 2-chloro group.
11. Substance according to claim 1, characterized in that R = R¹ represent H, and R² represents 4-fluoro group.
12. Substance according to claim 1, characterized in that R = R¹ represent H, and R² represents 4-methyl group.
13. Substance according to claim 1, characterized in that R = R¹ represent H, and R² represent 2-methyl group.
14. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group and R² represents H.
15. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, and R² represents 4-chloro group.
16. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, and R² represents 2-chloro group.
17. Substance according to claim 1, characterized in that represents cladinosyl group, R¹ represents β-cyanoethyl group, and R² represents 4-fluoro group.
18. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, and R² represents 4-methyl group.

19. Substance according to claim 1, characterized in that R represents cladinosyl group, R¹ represents β-cyanoethyl group, and R² represents 2-methyl group.
20. Substance according to claim 1, characterized in that R = R² represents H, and R¹ represents β-cyanoethyl group.
21. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl group, and R² represents 4-chloro group.
22. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl group, and R² represents 2-chloro group.
23. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl group, and R² represents 4-fluoro group.
24. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl group, and R² represents 4-methyl group.
25. Substance according to claim 1, characterized in that R represents H, R¹ represents β-cyanoethyl group, and R² represents 2-methyl group.
26. Process for the preparation of 9a-N-[N'-(benzenesulfonyl)carbamoyl-γ-aminopropyl] and 9a-N-[N'-(β-cyanoethyl)-N'-(benzenesulfonyl)carbamoyl-γ-aminopropyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula 1,



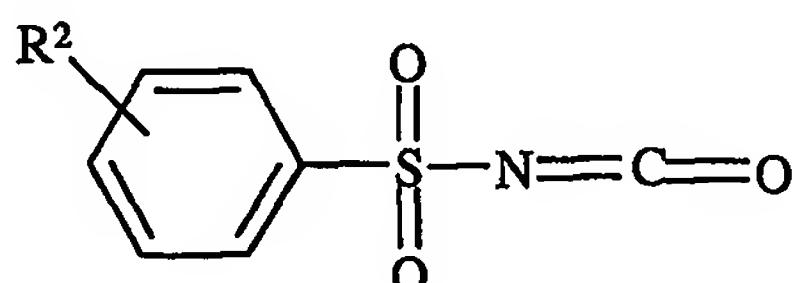
1

wherein R represents H or cladinosyl group, R¹ represents H or β-cyanoethyl group, and R² represents H or fluoro, chloro and methyl group, characterized in that
9a-N-(γ-aminopropyl) and *9a-N-[N'-(β-cyanoethyl)-γ-aminopropyl]* derivatives of 9-deoxo-
-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-
-9a-aza-9a-homoeithronolide A general formula 2,



2

wherein R represents H and cladinosyl group and R¹ represents H and β-cyanoethyl group is reacted with substituted phenylsulfonylisocyanate general formula 3



3

wherein R² represents H, chloro, fluoro and methyl group, in toluene, xylene or some other aprotic solvents, at a temperature 0°-110°C and then, if appropriate, to a reaction with inorganic or organic acids.

27. Pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antibacterially effective amount of the substances according to claim 1.
28. Use of a substance according to any claims 1 to 25 for preparing compositions for sterilization rooms and medical instruments as well as for protection of wall and wooden coatings.

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07H17/08 C07H17/00 A61K31/7048 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/068438 A (BUKVIC KRAJACIC MIRJANA ; KUJUNDZIC NEDJELJKO (HR); PLIVA D D (HR);) 6 September 2002 (2002-09-06) abstract -----	1,27
A	WO 00/66603 A (MARU & SCARON ; MUTAK STJEPAN (HR); KUJUND & ZCARON (HR); MAR & SCA) 9 November 2000 (2000-11-09) abstract -----	1,27

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

13 April 2004

Date of mailing of the international search report

26/04/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

de Nooy, A

Information on patent family members

Int'l Application No

PCT/HR 03/00057

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 02068438	A	06-09-2002	HR CZ WO HU SK	20010146 A1 20032216 A3 02068438 A2 0303319 A2 12112003 A3	31-12-2002 12-11-2003 06-09-2002 28-01-2004 02-12-2003
WO 0066603	A	09-11-2000	HR AT AU AU BG BR CA CN CZ DE DK EE EP WO HU JP NO NZ PL PT SI SK TR ZA	990130 A1 244258 T 767681 B2 4135000 A 106173 A 0010231 A 2372977 A1 1351606 T 20013913 A3 60003671 D1 1175429 T3 200100582 A 1175429 A1 0066603 A1 0201146 A2 2002543213 T 20015346 A 515278 A 351402 A1 1175429 T 1175429 T1 15702001 A3 200103143 T2 200108484 A	31-10-2001 15-07-2003 20-11-2003 17-11-2000 31-07-2002 19-02-2002 09-11-2000 29-05-2002 17-04-2002 07-08-2003 20-10-2003 17-02-2003 30-01-2002 09-11-2000 29-07-2002 17-12-2002 01-11-2001 30-06-2003 07-04-2003 28-11-2003 31-12-2003 04-04-2002 22-04-2002 16-01-2003